

Synthetic use of the primary kinetic isotope effect in hydrogen atom transfer: generation of α -aminoalkyl radicals†

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The extent to which deuterium can act as a protecting group to prevent unwanted 1,5-hydrogen atom transfer to aryl and vinyl radical intermediates was examined in the context of the generation of α -aminoalkyl radicals in a pyrrolidine ring. Intra- and intermolecular radical trapping following hydrogen atom transfer provides an illustration of the use of the primary kinetic isotope effect in directing the outcome of synthetic C–C bond-forming processes.

Introduction

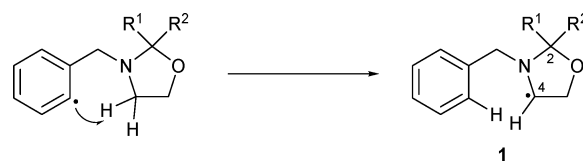
Traditionally, the observation of a primary kinetic isotope effect (or lack thereof) has provided an excellent, straightforward probe for the examination of reactions whose mechanisms involve the cleavage of a carbon–hydrogen bond. The magnitude of the isotope effect observed gives an estimate of the extent of hydrogen atom transfer in the transition state, thus providing insight into the rate-determining step of the reaction.¹ In some instances, the substitution of a hydrogen atom with deuterium may even be sufficient to divert a reaction predominantly along an alternative, normally minor pathway.² There are, however, comparatively few examples of this phenomenon being applied to routine synthetic procedures.

Clayden *et al.* have shown that the replacement of hydrogen with deuterium at positions of high kinetic acidity in benzamides can result in selectivity in the regiochemical course of deprotonation reactions with organolithium reagents, a deuterium atom effectively acting as a “protecting group” for a carbon–hydrogen bond.³ Prior to this, Miyano reported the use of deuterium to invert the *exo/endo* selectivity in the generation of an alkene by a thionyl chloride-induced β -elimination of a 1-methylcyclobutanol moiety, as a key step in the synthesis of 18-oxoprogesterone,⁴ and both Vedejs and Little⁵ and Danishefsky *et al.*⁶ have also used deuterium to prevent unwanted intramolecular deprotonation by key intermediate organolithium species (originally intended to act as nucleophiles) in cyclisation procedures.

Herein, we discuss the background to and provide the full experimental details of some of our recent studies⁷ into the extent to which deuterium can be used to protect carbon–hydrogen bonds in radical procedures involving hydrogen atom transfer.⁸

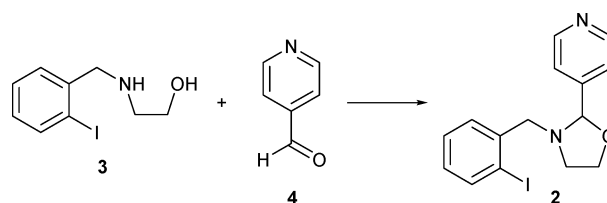
Results and discussion

Our earlier studies into the preparation of highly substituted β -amino alcohols utilised a radical-based synthetic pathway, in which the key step was the generation of a 1,3-oxazolidine-derived C4 α -aminoalkyl radical **1** via a 1,5-hydrogen atom transfer step (Scheme 1).⁹



Scheme 1 α -Aminoalkyl radical generation by 1,5-hydrogen atom transfer.

During the course of this work, we encountered a problem with the regioselectivity of hydrogen atom transfer in the remote functionalisation process. Whilst attempting to maximise the stereoselectivity of the trapping of the intermediate radicals **1** at C-4, using the principle of “self-regeneration of stereocentres,”¹⁰ we examined the radical reactions of a racemic, aldehyde-derived 1,3-oxazolidine **2** (with a large difference in C2 substituent size), prepared from 2-(2-iodobenzylamino)ethanol **3** and 4-pyridinecarboxaldehyde **4** (Scheme 2). Although the aldehyde-derived 1,3-oxazolidines such as **2** were found to be more robust towards hydrolytic cleavage (particularly during the commonly non-trivial chromatographic purification of radical reaction products) than the ketone-derived species used in earlier work,⁹ this substrate obviously introduced the issue of C2 *vs.* C4 regioselectivity in the hydrogen atom transfer, occurring after initial aryl radical generation.



Scheme 2 Reagents and conditions: MgSO_4 , THF, rt, 18 h (85%).

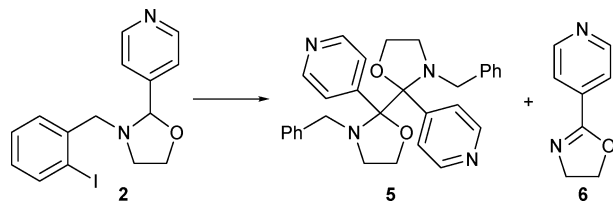
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On reducing the aryl iodide moiety in **2** with tributyltin hydride (under standard conditions with AIBN as initiator), only two heterocyclic products could be isolated after repeated chromatography of the crude reaction product, required to remove all tin-containing residues. (The remainder of the material appeared to be a complex mixture of degradation products.) These products were identified as the C2-linked dimeric bioxazolidine **5** and the dihydrooxazole **6**, isolated in very low (8 and 3%, respectively) yields (Scheme 3).



Scheme 3 Reagents and conditions: Bu₃SnH (4.1 equiv.), AIBN (0.1 equiv.), C₆H₆, 80 °C, 18 h (**5**, 8%; **6**, 3%).

Both products had clearly arisen from the formation of the highly stabilised C2 radical intermediate **7** (Fig. 1) by either β -elimination of a benzyl radical for the formation of **6** or radical–radical combination in the case of **5**. No products could be identified as being derived from the required intermediate C4 radical **8** (Fig. 1).

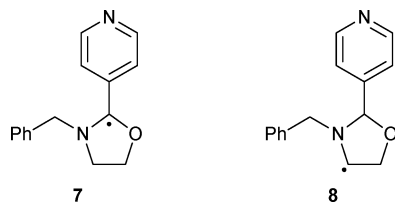


Fig. 1 Intermediate α -aminoalkyl radicals derived from **2**.

Despite the small quantity of material obtained, we were fortunate enough to be able to obtain an X-ray crystal structure of dimer **5**, thus providing confirmation of the product structure (Fig. 2).

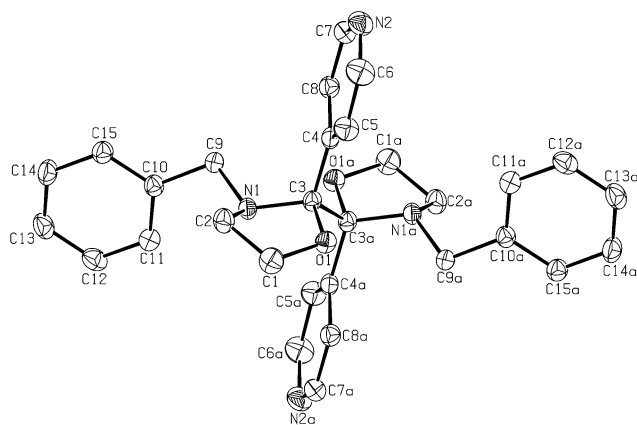
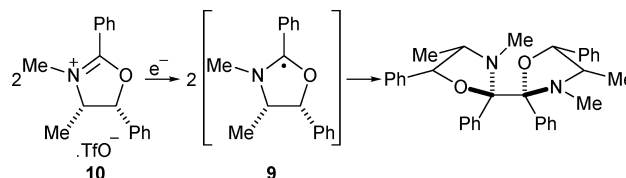


Fig. 2 ORTEP representation of **5**; ellipsoids drawn at 30% probability level.

Interestingly, Shono *et al.* have demonstrated an essentially identical dimerisation of oxazolidine C2 radicals such as **9**, derived

from single electron reduction of a 2-aryl-2-oxazolinium salt **10** (Scheme 4).¹¹ Our observation of apparently exclusive formation of the *meso*-diastereoisomer of the dimer **5** is in contrast to the stereoselectivity proposed by Shono *et al.* (Scheme 4), although the reasons for this stereoselectivity are unclear. Indeed, it is not unfeasible that we were only able to isolate the minor diastereoisomer of **5**, with the major *2R,2'R/2S,2'S* racemic mixture possibly being labile under the reaction and/or purification conditions. The ¹H NMR spectrum of **5** also revealed a remarkable *ca.* 2 ppm chemical shift difference between the diastereotopic methylene group protons at the benzylic and oxazolidine C4/C5 positions, as can be seen in the portion of the spectrum shown in Fig. 3.



Scheme 4 Reductive coupling of 2-aryl-2-oxazolinium salts.¹¹

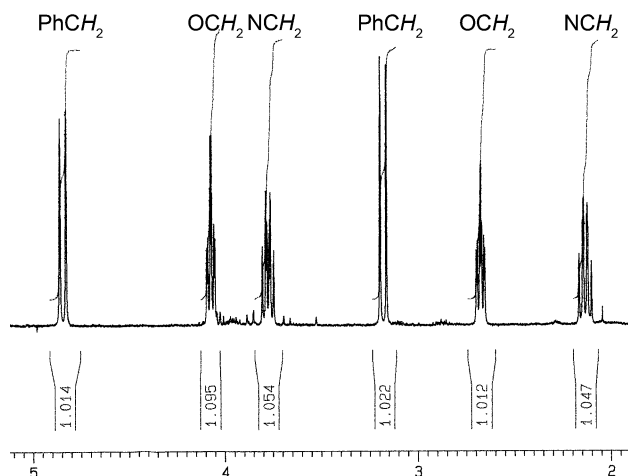
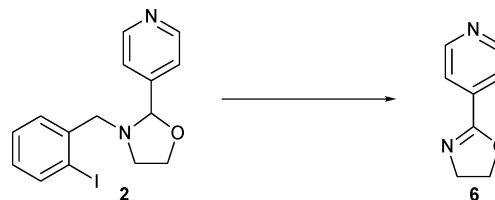


Fig. 3 400 MHz ¹H NMR spectrum of **5**.

From previous studies,⁹ we were confident that should the desired intermediate C4 α -aminoalkyl radical **8** be formed during the hydrogen atom transfer step, we should be able to trap it with an appropriate radicalphile. To this end, we therefore carried out a tributyltin hydride reduction of **2** in the presence of a 3-fold excess of *tert*-butyl acrylate (Scheme 5).

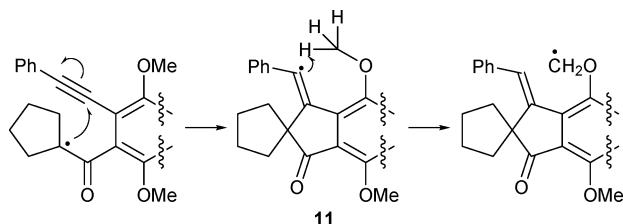


Scheme 5 Reagents and conditions: *tert*-butyl acrylate (3.0 equiv.), Bu₃SnH (3.5 equiv.), AIBN (0.5 equiv.), C₆H₆, 80 °C, 23 h, (59%).

Surprisingly, this reaction gave the dihydrooxazole **6** as the only isolable product, in a 59% yield, again suggesting efficient and apparently exclusive formation of the undesired C2 radical

intermediate **7**. At this stage, therefore, we were faced with a difficult regiochemical problem to solve in our key hydrogen atom transfer step.

During studies ultimately leading to the successful total synthesis of fredericamycin A, an antibiotic with antitumour activity, Clive *et al.* experienced similar problems with unwanted 1,6-hydrogen atom transfer from an aryl methyl ether (used as a phenol protecting group) to a vinyl radical **11**, generated from a 5-*exo dig* spirocyclisation (Scheme 6).¹²



Scheme 6 Unwanted 1,6-hydrogen atom transfer in fredericamycin A synthesis.¹²

Deuteration of this methyl ether was found to retard this hydrogen atom transfer sufficiently to ensure that the intermediate vinyl radical **11** was trapped with triphenyltin hydride before the problematic side reaction could occur.¹³ Encouraged by this observation, we decided to investigate the reactivity of a C2 deuterated version of our 1,3-oxazolidine radical precursor **12** (Fig. 4).

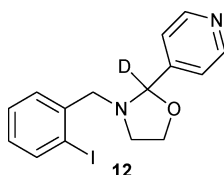
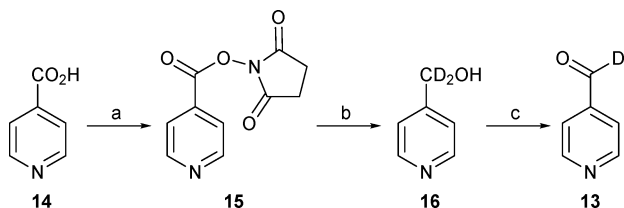


Fig. 4 C2 deuterated 1,3-oxazolidine radical precursor.

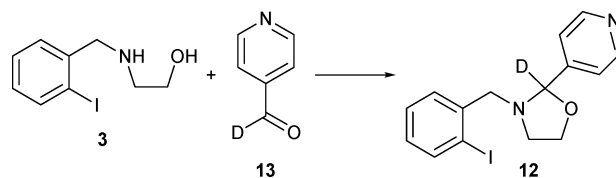
In order to access **12**, α -deutero-4-pyridinecarboxaldehyde **13** was firstly prepared by a three-step process. Isonicotinic acid **14** was converted into an active ester **15** by an EDCI-mediated coupling with *N*-hydroxysuccinimide.¹⁴ Reduction of **15** with an excess of sodium borodeuteride gave the corresponding di-deuterated alcohol **16** which was then oxidised to the required aldehyde **13** under standard Swern conditions (Scheme 7).



Scheme 7 Reagents and conditions: (a) *N*-hydroxysuccinimide, EDCI, DMF, 0 °C, 2 h, (60%); (b) NaBD₄ (4.0 equiv.), EtOH, rt, 18 h (98%); (c) DMSO (2.2 equiv.), (COCl)₂ (1.1 equiv.), CH₂Cl₂, –60 °C, 2 min, then **16**, –60 °C, 15 min, then Et₃N (5 equiv.), –60 °C, 5 min, then warm to rt (55%).

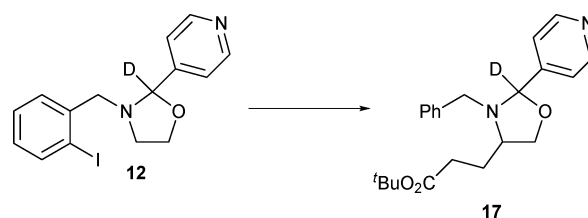
The overall yield of **13** from isonicotinic acid **14** was 32%, with the level of deuteration being at least 98%. Condensation of **13**

with 2-(2-iodobenzylamino)ethanol **3** under previously developed conditions,⁹ gave **12** in an excellent (89%) yield (Scheme 8).



Scheme 8 Reagents and conditions: MgSO₄, THF, rt, 18 h (89%).

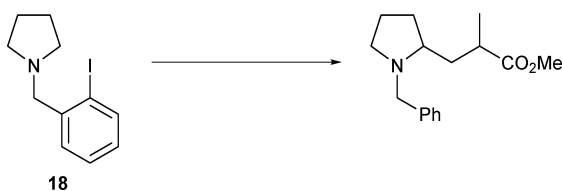
In contrast to the results obtained with 1,3-oxazolidine substrate **2**, on subjecting **12** to reduction with tributyltin hydride in the presence of a 3-fold excess of *tert*-butyl acrylate, this time with initiation using triethylborane,¹⁵ we obtained the desired C-4 alkylated derivative **17** as the sole heterocyclic species from the crude reaction product (Scheme 9). This was obtained in a poor (13%) yield as a 6.5:1 ratio of inseparable diastereoisomers but most importantly, neither the dihydrooxazole **6** nor the bioxazolidine dimer **5** appeared to be produced, suggesting that hydrogen atom transfer to give the unwanted C2 radical **7** had been significantly suppressed as required.



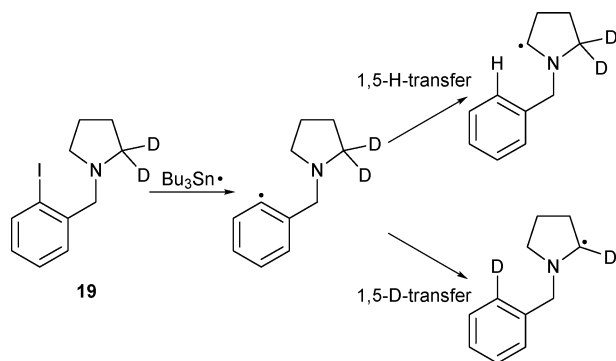
Scheme 9 Reagents and conditions: *tert*-butyl acrylate (3.0 equiv.), Bu₃SnH (3.5 equiv.), Et₃B (0.2 equiv.), C₆H₆, rt, 18 h (13%).

Although at this stage we had identified an alternative solution to our problem of regioselectivity of hydrogen atom transfer in 1,3-oxazolidines by using 2-iodobenzamide derivatives,¹⁶ the importance of α -aminoalkyl radicals in synthesis¹⁷ prompted us to undertake a more detailed, fundamental investigation into the effectiveness of deuterium in controlling the selectivity of this process. It is well established that quantum mechanical tunnelling can provide the principal mechanism for hydrogen atom transfer, resulting in much higher kinetic isotope effects than would have been predicted from a simple zero-point energy model, adding to the potential synthetic utility of such an approach.¹⁸ We therefore felt it appropriate and important to assess the efficiency of deuterium as a “blocking group” in synthetically useful scenarios in a systematic manner.⁷

Our interest in the generation of α -aminoalkyl radicals via 1,5-hydrogen atom transfer highlighted studies carried out by Undheim *et al.* which investigated the radical-based α -alkylation of a number of nitrogen-containing heterocycles. Of particular relevance was the remote functionalisation of *N*-(2-iodobenzyl)pyrrolidine **18** shown in Scheme 10.¹⁹ Our initial investigations were aimed at assessing the degree of selectivity (and hence, the extent of the kinetic isotope effect) between 1,5-hydrogen atom transfer and the competitive deuterium transfer in the di-deuterated analogue **19** of Undheim *et al.*'s radical reaction substrate **18** (Scheme 11).

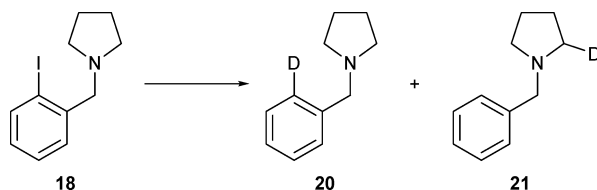


Scheme 10 Reagents and conditions: methyl methacrylate (3.2 equiv.), Bu₃SnH (2.0 equiv.), AIBN (0.1 equiv.), C₆H₆, 80 °C, 9 h (66%).²⁰



Scheme 11 1,5-Hydrogen vs. deuterium atom transfer.

Having found in earlier studies with 1,3-oxazolidine substrates that the rate of 1,5-hydrogen atom transfer was sufficiently high that slow addition of tributyltin hydride and the radical initiator was not necessary,⁹ we firstly confirmed that this was also the case in the pyrrolidine system **18** by carrying out its reduction with tributyltin deuteride. (Scheme 12; the reduction was carried out with 2.0 equiv. of tributyltin deuteride at a substrate concentration of 58 mM.)

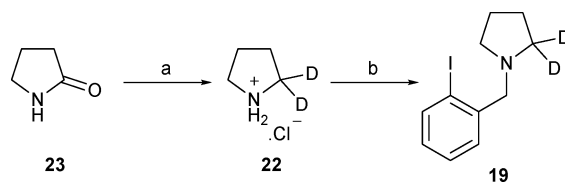


Scheme 12 Reagents and conditions: Bu₃SnD (2.0 equiv.), AIBN (2.3 equiv.), C₆H₆, 80 °C, 6 h (23%; **20**:**21**, 1 : 19).

As is often the case, the repeated chromatography required for removal of the organotin residues from the reaction products resulted in a disappointing (23%) final isolated yield of the **20/21** product mixture. Fortunately, the product ratios could also be verified if required using ²H NMR spectroscopy on the crude reaction product, the 1 : 19 ratio of **20** : **21** being confirmed before and after chromatography.[‡] With 95% of the isolable reaction product originating from 1,5-hydrogen atom transfer, the high efficiency of this process was confirmed and similar conditions were used for all future radical reactions.

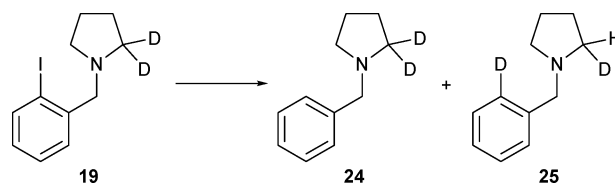
The required di-deuterated substrate **19** was prepared using 2,2-dideuteropyrrolidine, isolated as its hydrochloride salt **22** from a lithium aluminium deuteride reduction of 2-pyrrolidinone **23**. After reaction with 2-iodobenzyl bromide in the presence of an

excess of Hünig's base, **19** was isolated in a 33% overall yield from **23** (Scheme 13).

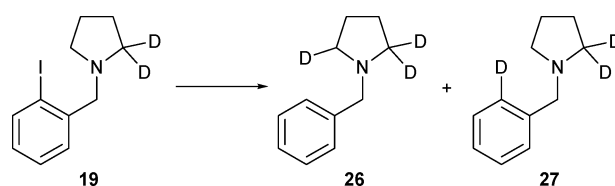


Scheme 13 Reagents and conditions: (a) LiAlD₄ (2.5 equiv.), THF, 0 °C then 67 °C, 14 h, then HCl, H₂O (62%); (b) 2-iodobenzyl bromide (1.1 equiv.), 'PrNEt₂ (4.0 equiv.), CH₃CN, rt, 14 h (53%).

19 was then subjected to reduction reactions using 1.3 equiv. of both tributyltin hydride (Scheme 14) and tributyltin deuteride (Scheme 15), at three different temperatures (80, 25 and –50 °C), in order to estimate the extent to which the primary kinetic isotope effect could determine the regioselectivity of the hydrogen atom transfer. All reactions were carried out at our standardised substrate concentration of 50–60 mM, with benzene as solvent for the reactions at 80 and 25 °C and fluorobenzene at –50 °C. With AIBN as initiator, thermal decomposition at 80 °C was replaced by photochemical radical generation at the lower temperatures, using a medium pressure mercury vapour lamp. Chromatographic purification of the reduced products **24–27** was carried out on silica gel containing potassium fluoride (10% w/w),²⁰ which was found to significantly improve the isolated yields when compared with the tributyltin deuteride reduction of **18**, and this purification method was also used very successfully in later experiments. Table 1 summarises the results of these studies.[‡]



Scheme 14 Reagents and conditions: Bu₃SnH (1.3 equiv.), AIBN (0.7–2.4 equiv.), C₆H₆ or C₆H₅F, heat or UV irradiation, 80, 25 or –50 °C, 6–12 h.



Scheme 15 Reagents and conditions: Bu₃SnD (1.3 equiv.), AIBN (2.1–2.4 equiv.), C₆H₆ or C₆H₅F, heat or UV irradiation, 80, 25 or –50 °C, 6–12 h.

The ambiguity in terms of the possible origins of compounds **24** (a product of direct reduction and/or 1,5-hydrogen atom transfer?) and **27** (a product of direct reduction and/or 1,5-deuterium atom transfer?) of course does not allow an accurate estimation of the actual *k_H*/*k_D* values from these experiments. The general preference for hydrogen atom transfer over deuterium atom transfer was, however, clear, as was the apparent increased

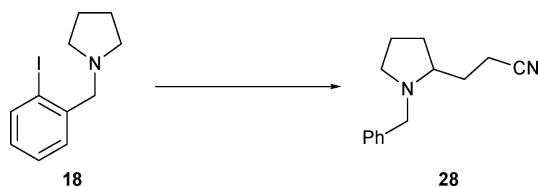
[‡] Product ratios were determined by a combination of ¹H and ²H NMR spectroscopy and mass spectrometry as appropriate.

Table 1 Product ratios and yields for reduction of **19**[‡]

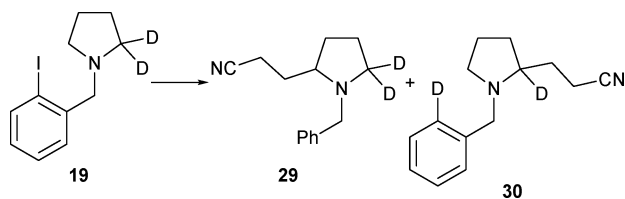
Entry	Bu ₃ SnH/D	T/°C	Products	Ratio	Yield (%)
1	H	80	24 , 25	3:1	55
2	H	25	24 , 25	12:1	58
3	H	−50	24 , 25	49:1	66
4	D	80	26 , 27	1:2	58
5	D	25	26 , 27	7:1	71
6	D	−50	26 , 27	7:1	55

selectivity for hydrogen transfer as the reaction temperature was lowered.

To investigate the degree to which deuterium “protection” of a carbon–hydrogen bond can be used to direct hydrogen atom transfer in a synthetically valuable carbon–carbon bond forming procedure, we chose the α -alkylation of the pyrrolidine moiety¹⁹ in radical precursor **18** as our starting point. Acrylonitrile was chosen as the radicalophile on the basis of its high relative rate for trapping of alkyl radicals compared with other electron-deficient alkenes such as acrylate esters.²¹ At a substrate concentration of 58 mM, **18** was reduced with tributyltin hydride in the presence of a 4.9-fold excess of acrylonitrile, with thermal AIBN initiation at 80 °C (Scheme 16). The α -alkylated derivative **28** was isolated as the only identifiable pyrrolidine-containing product, in a synthetically viable 56% yield.

**Scheme 16** Reagents and conditions: Bu₃SnH (2.0 equiv.), acrylonitrile (4.9 equiv.), AIBN (2.1 equiv.), C₆H₆, 80 °C, 6 h (56%).

The same methodology was then transferred to di-deuterated substrate **19**. Again the temperatures chosen were 80, 25 and −50 °C, with a change of solvent to fluorobenzene for the −50 °C experiment and photochemical AIBN initiation at both 25 and −50 °C (Scheme 17).

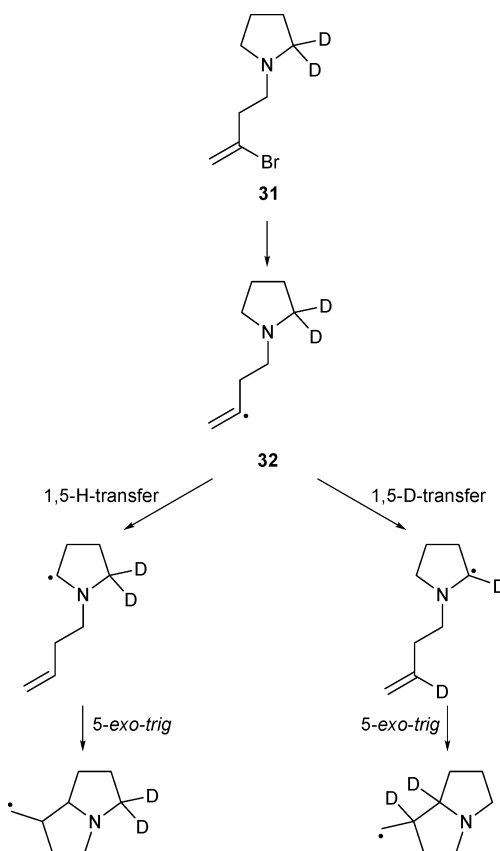
**Scheme 17** Reagents and conditions: Bu₃SnH (2.0 equiv.), acrylonitrile (5.0–5.8 equiv.), AIBN (2.0–2.4 equiv.), C₆H₆ or C₆H₅F, heat or UV irradiation, 80, 25 or −50 °C, 6 h.

The results, summarised in Table 2, show a clear trend, with the maximum primary kinetic isotope effect of $k_H/k_D = 5.7$ being observed at −50 °C (entry 3) and the value dropping to 3.2 at 80 °C (entry 1).[‡] The deviation from the normally expected maximum value of $k_H/k_D \sim 7$ –8 is probably best rationalised by invoking a later, more “product-like” transition state for the hydrogen transfer process, stabilised by the adjacent nitrogen atom.

Table 2 Product ratios and yields for acrylonitrile trapping experiments[‡]

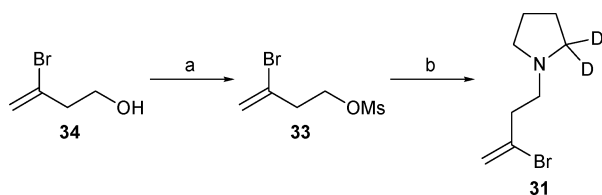
Entry	T/°C	Ratio 29 : 30	Yield (%)
1	80	3.2:1	15
2	25	4.5:1	23
3	−50	5.7:1	56

To further extend these studies to include intramolecular α -aminoalkyl radical trapping, an α -dideuterated analogue **31** of the radical precursor used by Robertson *et al.* for the synthesis of (\pm)-heliotridane²² was then prepared. This substrate contains an appropriately positioned vinyl group for a 5-*exo-trig* cyclisation to follow 1,5-hydrogen (or deuterium) atom transfer to intermediate vinyl radical **32** (Scheme 18).

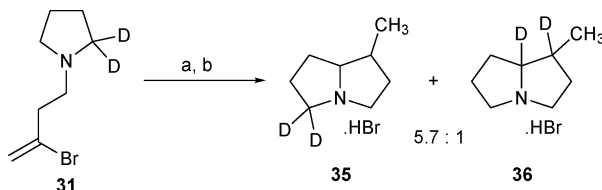
**Scheme 18** Intramolecular radical trapping after 1,5-hydrogen or deuterium transfer.

31 was prepared by the *N*-alkylation of 2,2-dideuteropyrrolidine hydrochloride **22** with 3-bromobut-3-enyl methanesulfonate **33**²³ (prepared from 3-bromobut-3-en-1-ol **34**²⁴), in the presence of potassium carbonate (Scheme 19).

At 80 °C, with an initial substrate concentration of 12 mM in benzene, **31** was reduced with a solution of tributyltin hydride and AIBN (also in benzene) added slowly over 1 h. Thiophenol was added to aid product purification²² and the two di-deuterated products **35** and **36** were isolated in a 5.7:1 ratio as their hydrobromide salts (30% overall yield, Scheme 20).[‡] Unfortunately, attempts to carry out the reaction at lower temperatures with



Scheme 19 Reagents and conditions: (a) $\text{CH}_3\text{SO}_2\text{Cl}$ (1.2 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2 , rt, 1 h (90%); (b) **22** (1.2 equiv.), K_2CO_3 (3.6 equiv.), CH_3CN , 82 °C, 24 h (28%).



Scheme 20 Reagents and conditions: (a) Bu_3SnH (2.7 equiv.), AIBN (0.2 equiv.), C_6H_6 , 80 °C, 3 h; (b) PhSH (3.2 equiv.) (30% over 2 steps).

photochemical initiation did not give any of the desired products, but the result obtained at 80 °C shows a significant preference for hydrogen rather than deuterium transfer to intermediate vinyl radical **32** with an apparent value of $k_{\text{H}}/k_{\text{D}} = 5.7$.

A small quantity of the non-cyclised reduction product **37** (Fig. 5) was also produced (9% yield) during this reaction and this could not be separated from the **35/36** mixture.

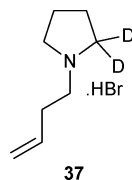


Fig. 5 1-(But-3-enyl)-2,2-dideuteropyrrolidine hydrobromide.

Conclusions

Successful implementation of 1,5-hydrogen atom transfer in the remote activation of carbon centres in synthetic methodologies involving radical intermediates, requires high regioselectivity. We have shown that for the generation of α -aminoalkyl radicals by such a process, deuterium can be used to block this atom transfer to a degree that could potentially be synthetically useful. The estimated values of $k_{\text{H}}/k_{\text{D}}$ observed in these experiments suggest the likelihood of a later, product radical-like transition state for this process.

In order to use such a “protecting group” strategy, based on the primary kinetic isotope effect, either (i) the products which would ultimately arise from the different hydrogen atom transfer processes would need to be different in structure and, therefore, separable; (ii) the blocking deuterium atom(s) would need to be incorporated into a removable protecting group (as exemplified by the earlier studies of Clive *et al.*¹³); or (iii) the deuterium atoms would need to be readily exchangeable with hydrogen if isotopic labelling of the final product were not desired.

Experimental

General experimental

Melting points were determined with a Gallenkamp MPD350 apparatus and are uncorrected.

Infrared spectra were recorded using a Nicolet Magna 550 spectrometer. Generally, only major absorbances are quoted, using the abbreviations: (for intensity) w, weak; m, medium; and s, strong, with br indicating a broad peak. Thin film samples were produced by evaporation of a dilute chloroform or dichloromethane solution of the sample on a sodium chloride plate.

^1H NMR spectra were recorded at 300 and 400 MHz using Bruker ACF300 and Avance DRX400 spectrometers, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, the residual solvent peak being used for referencing purposes where possible. Coupling constants are quoted to the nearest 0.5 Hz with peak multiplicities for single resonances being labelled as: s, singlet; d, doublet; t, triplet; q, quartet; m, unresolved multiplet; AB, AB pattern; AA'BB', AA'BB' pattern and br, broad. Where delineation of individual resonances is not possible, the relevant peaks are grouped together, over a chemical shift range, as complex.

^{13}C NMR spectra were recorded at 75 and 100 MHz using Bruker ACF300 and Avance DRX400 spectrometers, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, the solvent peak being used for referencing. Where necessary, DEPT editing was used for assignment purposes.

^2H NMR spectra were recorded at 61.4 MHz using a Bruker DRX400 spectrometer. Where possible, the natural abundance deuterium resonance from the protonated solvent was used for referencing.

Mass spectra were obtained using Thermoquest Finnigan Trace 2000 GC-MS and Micromass GCT instruments or by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK. Ionisation modes are labelled as: EI, electron impact; CI, chemical ionisation and ES^+ , positive ion electrospray.

X-Ray crystallographic data were recorded on a Nonius Kap-paCCD diffractometer driven by COLLECT²⁵ and DENZO²⁶ software. The structure was determined using the direct methods procedure in SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97.²⁷ Full details of data collection and structure determination have been deposited with the Cambridge Crystallographic Data Centre with deposition number CCDC 291244.[†]

Analytical thin layer chromatography was carried out using Merck Kieselgel 60 F₂₅₄, coated on aluminium plates, with visualisation of spots by quenching of UV (254 nm) fluorescence or staining with iodine or alkaline potassium permanganate solution as appropriate. Silica gel with particle size 40–63 μm was used for flash chromatography.

Solvents and reagents were used as commercially supplied or, when necessary, purified using standard procedures detailed in *Purification of Laboratory Chemicals*, 3rd edn, W. L. F. Armarego and D. D. Perrin, Pergamon Press, Oxford, 1998. The fraction of light petroleum ether boiling in the range 40 to 60 °C is referred to as “petroleum ether.”

A Büchi R110 Rotovapor was used for the removal of solvents under reduced pressure, with a water or dry ice condenser being used as appropriate.

3-(2-Iodobenzyl)-2-(pyridin-4-yl)oxazolidine (2)

4-Pyridinecarboxaldehyde **4** (610 μL , 6.4 mmol) was added to a stirred solution of 2-(2-iodobenzylamino)ethanol⁹ **3** (2.00 g, 7.2 mmol) in tetrahydrofuran (50 cm^3) containing anhydrous magnesium sulfate (2.00 g, 16.6 mmol), under a nitrogen atmosphere. After stirring for 18 h, the reaction mixture was filtered, the solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate (30 cm^3). The resulting solution was washed with aqueous sodium metabisulfite solution (20% w/v, 5 \times 10 cm^3), dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **2** (2.25 g, 85%) as a yellow oil (Found MH^+ (CI) 367.0299, $\text{C}_{15}\text{H}_{16}\text{IN}_2\text{O}$ requires 367.0307); ν_{max} (thin film)/ cm^{-1} 3112–2767 (m) (C–H), 1599 (s), 1562 (w), 1466 (m), 1437 (m), 1410 (s), 1385 (w), 1342 (m), 1317 (m), 1234 (m), 1200 (w), 1159 (w), 1124 (m), 1101 (m), 1063 (s), 1036 (s), 1013 (s), 993 (m), 904 (w), 814 (m), 784 (m), 752 (s) and 638 (m); δ_{H} (400 MHz; CDCl_3) 2.88 (1H, m, NCHHCH_2), 3.08 (1H, m, NCHHCH_2), 3.76, 3.86 (2 \times 1H, AB, $J = 14$, ArCH_2), 3.96 (1H, m, CHHO), 4.07 (1H, m, CHHO), 5.27 (1H, s, NCHO), 6.95 (1H, dt, $J = 1.5$ and 7.5 , arylCH), 7.31 (1H, dt, $J = 1$ and 7.5 , arylCH), 7.41–7.47 (3H, complex, arylCH and 2 \times pyridineCH), 7.83 (1H, dd, $J = 1$ and 8 , arylCH) and 8.56 (2H, part of AA'BB' , $J = 6$, pyridineCH); δ_{C} (100 MHz; CDCl_3) 51.2 (NCH_2CH_2), 61.7 (CH_2O), 64.6 (ArCH_2), 95.4 (NCHO), 100.1 (arylCI), 122.2 (pyridineCH), 128.2, 129.1, 130.2, 139.7 (arylCH), 140.5 (aryl ipsoC) and 149.8 (pyridineCH); m/z (EI) 366 (M^+ , 3%), 288 (100), 217 (85), 149 (12), 135 (19), 119 (25), 91 (68), 90 (66), 89 (43), 78 (32), 77 (22), 65 (33), 63 (25), 51 (40) and 39 (26); m/z (CI) 367 (MH^+ , 11%), 241 (21), 149 (100), 134 (12), 108 (31), 107 (23), 106 (17), 94 (43), 80 (19) and 72 (9).

3,3'-Dibenzyl-2,2'-di(pyridin-4-yl)-2,2'-bioxazolidine (5)

Tributyltin hydride (840 μL , 3.1 mmol) was added to a stirred, degassed solution of 3-(2-iodobenzyl)-2-(pyridin-4-yl)oxazolidine **2** (275.6 mg, 0.75 mmol) and 2,2'-azobisisobutyronitrile (12.0 mg, 73.1 μmol) in benzene (50 cm^3). After stirring under reflux under a nitrogen atmosphere for 18 h, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (50% petroleum ether–50% ethyl acetate) to give **5** (15.1 mg, 8%) as a pale yellow, crystalline solid (Found MH^+ (CI) 479.2439, $\text{C}_{30}\text{H}_{31}\text{N}_4\text{O}_2$ requires 479.2447); ν_{max} (thin film)/ cm^{-1} 3127–2783 (m) (C–H), 1734 (m), 1635 (s), 1549 (w), 1497 (w), 1456 (m), 1426 (m), 1410 (m), 1369 (w), 1281 (s), 1217 (w), 1124 (w), 1065 (m), 833 (w), 756 (s), 700 (m) and 667 (m); δ_{H} (400 MHz; CDCl_3) 2.14 (2H, m, 2 \times NCHHCH_2), 2.68 (2H, 2 \times CHHO), 3.18, 4.84 (2 \times 2H, AB, $J = 13$, 2 \times PhCH_2), 3.78 (2H, m, NCHHCH_2), 4.07 (2H, m, CHH_2O), 6.83–6.88 (4H, complex, phenylCH), 7.13–7.18 (6H, complex, phenylCH) and 7.76, 8.71 (2 \times 4H, AA'BB' , $J = 6$, pyridineCH); δ_{C} (100 MHz; CDCl_3) 48.3 (NCH_2CH_2), 53.6 (CH_2O), 66.1 (PhCH_2), 99.2 (NCO), 124.3 (pyridineCH), 126.8, 127.7, 128.2 (phenylCH), 139.2 (phenyl ipsoC), 148.0 (pyridine *ipsoC*) and 149.0 (pyridineCH); m/z (EI) 239 (3%), 162 (18), 148 (14), 118 (27) and 106 (21), 91 (100), 84 (24), 78 (30), 65 (19), 51 (39), 49 (41) and 41 (23); m/z (CI) 479 (MH^+ , 1%), 241 (23), 239 (15), 149 (100), 134 (18), 108 (18), 106 (17), 94 (15) and 80 (25). A second fraction contained 2-(pyridin-4-yl)-4,5-dihydrooxazole **6** (3.8 mg, 3%), obtained as an orange oil (Found MH^+ (ES^+) 149.0716, $\text{C}_8\text{H}_9\text{N}_2\text{O}$ requires 149.0715); ν_{max} (thin film)/ cm^{-1} 3128–

2774 (m) (C–H), 1653 (s), 1601 (s), 1558 (m), 1497 (w), 1412 (s), 1367 (s), 1265 (s), 1217 (s), 1094 (m), 1080 (m), 1065 (m), 995 (w), 976 (w), 945 (s), 905 (w), 837 (m), 754 (s), 676 (s) and 667 (s); δ_{H} (400 MHz; CDCl_3) 4.09 (2H, t, $J = 9.5$, CH_2N), 4.46 (2H, t, $J = 9.5$, CH_2O) and 7.77, 8.70 (2 \times 2H, AA'BB' , $J = 6$, pyridineCH); δ_{C} (100 MHz; CDCl_3) 55.1 (CH_2N), 68.0 (CH_2O), 121.9 (pyridineCH), 135.1 (pyridine *ipsoC*), 150.2 (pyridineCH) and 163.0 ($\text{N} = \text{C}=\text{O}$); m/z (EI) 148 (M^+ , 37%), 118 (100), 91 (32), 84 (35), 78 (44), 51 (60), 49 (53) and 40 (35); m/z (CI) 166 (MNH_4^+ , 8%) and 149 (MH^+ , 100).

Crystal structure determination for compound 5

Crystal data at 120(2) K with Mo-K α ($\lambda = 0.71073$ Å). **5**: $M = 478.58$, monoclinic, $P2_1/c$, $a = 8.9276(2)$, $b = 14.35482(2)$, $c = 10.1033(4)$ Å, $\beta = 109.570(2)^\circ$, $V = 1236.42(7)$ Å³, $Z = 2$, 8639 measured reflections, 2801 unique reflections ($R_{\text{int}} = 0.0467$), $R = 0.0412$, $wR = 0.1158$.

2-(Pyridin-4-yl)-4,5-dihydrooxazole (6)

tert-Butyl acrylate (240 μL , 1.64 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-(pyridin-4-yl)oxazolidine **2** (200 mg, 0.55 mmol) in degassed benzene (10 cm^3) and the resulting solution was heated to reflux under a nitrogen atmosphere. A solution of tributyltin hydride (510 μL , 1.90 mmol) and 2,2'-azobisisobutyronitrile (44.8 mg, 0.27 mmol) in degassed benzene (10 cm^3) was added dropwise (using a syringe pump) over a period of 5 h, after which time heating under reflux was continued for a further 18 h. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (ethyl acetate) to give **6** (47.6 mg, 59%) as an orange oil. Data as reported above.

2,5-Dioxopyrrolidin-1-yl isonicotinate (15)¹⁴

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (5.00 g, 26.1 mmol) was added to a stirred solution of isonicotinic acid **14** (3.21 g, 26.1 mmol) in *N,N*-dimethylformamide (60 cm^3) at 0 $^\circ\text{C}$, followed by *N*-hydroxysuccinimide (3.00 g, 26.1 mmol). After stirring at this temperature for 2 h, the reaction mixture was poured into ethyl acetate (70 cm^3) and the resulting solution was washed successively with water (30 cm^3), saturated aqueous sodium bicarbonate solution (30 cm^3) and saturated aqueous sodium chloride solution (30 cm^3). The separated organic phase was then dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **15** (3.47 g, 60%) as a white, crystalline solid (Found MH^+ (ES^+) 221.0560, $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_4$ requires 221.0562); mp 115–120 $^\circ\text{C}$; ν_{max} (KBr disc)/ cm^{-1} 3331–2806 (s) (C–H), 1782 (m) (C=O), 1716 (s) (C=O), 1614 (w), 1521 (w), 1475 (w), 1412 (m), 1336 (w), 1306 (m), 1215 (s), 1078 (s), 1027 (s), 944 (m), 930 (m) and 856 (m); δ_{H} (400 MHz; CDCl_3) 2.93 (4H, s, CH_2CH_2) and 7.94, 8.88 (2 \times 2H, AA'BB' , $J = 6$, pyridineCH); δ_{C} (100 MHz; CDCl_3) 25.7 (CH_2CH_2), 123.2 (pyridineCH), 132.6 (pyridine *ipsoC*), 151.0 (pyridineCH), 160.8 (ester $\text{C} = \text{O}$) and 168.6 (imide $\text{C} = \text{O}$); m/z (EI) 220 (MH^+ , 1%), 106 (100), 78 (79), 51 (63), 50 (33) and 42 (9); m/z (CI) 221 (MH^+ , 88%), 141 (12), 138 (51), 124 (100), 123 (32), 108 (8), 91 (16), 80 (41) and 74 (9).

1,1-Dideutero(pyrid-4-yl)methanol (**16**)

2,5-Dioxopyrrolidin-1-yl isonicotinate **15** (1.00 g, 4.6 mmol) was added to a stirred solution of sodium borodeuteride (98 atom% D, 760 mg, 18.2 mmol) in ethanol at room temperature and stirring was continued at this temperature for 18 h. The solvent was removed *in vacuo* and the crude product was partitioned between water (40 cm³) and ethyl acetate (30 cm³), the separated aqueous phase being extracted with ethyl acetate (2 × 30 cm³). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **16** (500 mg, 98%) as a yellow oil (Found MH⁺ (CI) 112.0729, C₆H₆D₂NO requires 112.0731); ν_{\max} (thin film)/cm⁻¹ 3315 (br, m) (O–H), 3086–2806 (m) (C–H), 1608 (m), 1417 (s), 1313 (w), 1216 (s), 1113 (w), 1061 (w), 1006 (w), 921 (w), 758 (s) and 688 (s); δ_{H} (400 MHz; CDCl₃) 2.72 (1H, br s, OH) and 7.29, 8.51 (2 × 2H, AA'BB', *J* = 6, pyridineCH); δ_{D} (61.4 MHz; CCl₄) 4.62 (s, CD₂OH); δ_{C} (100 MHz; CDCl₃) 121.2 (pyridineCH), 149.5 (pyridineCH) and 150.4 (pyridine *ipso*C); *m/z* (EI) 111 (M⁺, 100%), 110 (92), 109 (31), 82 (56), 81 (94), 51 (53) and 40 (19); *m/z* (CI) 129 (MNH₄⁺, 3%), 112 (MH⁺, 100), 96 (66), 95 (14) and 80 (7).

α -Deutero-4-pyridinecarboxaldehyde (**13**)

A solution of dimethyl sulfoxide (570 μ l, 8.0 mmol) in dichloromethane (10 cm³) was added slowly, over a period of 5 min, to a stirred solution of oxalyl chloride (360 μ l, 4.1 mmol) in dichloromethane (10 cm³) at –60 °C, under a nitrogen atmosphere. After stirring at this temperature for a further 2 min, a solution of 1,1-dideutero(pyrid-4-yl)methanol **16** (410 mg, 3.7 mmol) in dichloromethane (10 cm³) was added slowly and after a further 15 min of stirring, triethylamine (2.58 cm³, 18.5 mmol) was also added slowly. Stirring was continued at –60 °C for a further 5 min and then the reaction mixture was allowed to attain room temperature before the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (40% dichloromethane–60% ethyl acetate) to give **13** (220 mg, 55%) as an orange oil (Found MH⁺ (CI) 109.0510, C₆H₅DNO requires 109.0512; ν_{\max} (thin film)/cm⁻¹ 3388–2791 (m) (C–H), 1697 (s) (C=O), 1675 (s), 1603 (s), 1563 (s), 1410 (s), 1388 (s), 1326 (w), 1302 (w), 1256 (m), 1223 (s), 1207 (s), 1196 (s), 1105 (s), 1061 (s), 992 (w), 945 (w), 889 (w), 854 (w), 789 (s), 722 (w), 667 (w) and 639 (s); δ_{H} (400 MHz; CDCl₃) 7.78, 8.86 (2 × 2H, AA'BB', *J* = 6, pyridineCH); δ_{D} (61.4 MHz; CCl₄) 10.1 (s, C(O)D); δ_{C} (100 MHz; CDCl₃) 122.1 (pyridineCH), 141.4 (pyridine *ipso*C), 151.2 (pyridineCH) and 191.1 (t, *J* = 30, C(O)D); *m/z* (EI) 108 (M⁺, 100%); 106 (43), 86 (19), 84 (32), 78 (50), 53 (40), 51 (94), 50 (52), 49 (70), 44 (42) and 43 (31); *m/z* (CI) 126 (MNH₄⁺, 10%), 109 (MH⁺, 100), 95 (35) and 80 (10).

3-(2-Iodobenzyl)-2-deutero-2-(pyridin-4-yl)oxazolidine (**12**)

α -Deutero-4-pyridinecarboxaldehyde **13** (210 mg, 1.9 mmol) was added to a stirred solution of 2-(2-iodobenzylamino)ethanol⁹ **3** (440 mg, 1.6 mmol) in tetrahydrofuran (30 cm³), containing anhydrous magnesium sulfate (2.00 g, 16.3 mmol), under a nitrogen atmosphere. After stirring for 18 h at room temperature, the reaction mixture was filtered, the solvent evaporated and the residue was purified by flash chromatography on silica gel (40% dichloromethane–60% ethyl acetate) to give **12** (520 mg, 89%) as

a dark orange oil (Found MH⁺ (ES⁺) 368.0366, C₁₅H₁₅DIN₂O requires 368.0370); ν_{\max} (thin film)/cm⁻¹ 3119–2741 (m) (C–H), 1599 (s), 1560 (m), 1466 (m), 1437 (m), 1408 (m), 1273 (m), 1234 (m), 1157 (m), 1065 (s), 906 (w), 818 (m), 787 (m), 752 (s) and 621 (m); δ_{H} (400 MHz; CDCl₃) 2.84–2.93 (1H, m, CHHN), 3.03 (1H, m, CHHN), 3.76, 3.86 (2 × 1H, AB, *J* = 14, ArCH₂), 3.96 (1H, *ca* q, *J* = 6, CHHO), 4.06 (1H, *ca* q, *J* = 6, CHHO), 6.95 (1H, dt, *J* = 2 and 7, arylCH), 7.31 (1H, t, *J* = 7, arylCH) and 7.40–8.92 (6H, complex, arylCH and pyridineCH); δ_{D} (61.4 MHz; CCl₄) 5.17 (s, CD), δ_{C} (100 MHz; CDCl₃) 51.2 (NCH₂CH₂), 61.7 (CH₂CH₂O), 64.6 (ArCH₂), 95.0 (m, CD), 100.1 (arylCI) 122.2, 128.2, 129.1, 130.2, 139.7 (arylCH and pyridineCH) 140.6 (aryl *ipso*CCH₂), 149.0 (pyridine *ipso*C) and 149.8 (pyridineCH); *m/z* (EI) 367 (M⁺, 4%), 289 (100), 217 (71), 120 (19), 91 (31), 90 (46), 89 (30) and 51 (22); *m/z* (CI) 368 (MH⁺, 84%), 242 (43) and 149 (100).

tert-Butyl-3-(3-benzyl-2-deutero-2-(pyridin-4-yl)oxazolidin-4-yl)propanoate (**17**)

Tributyltin hydride (510 μ l, 1.90 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-deutero-2-(pyridin-4-yl)oxazolidine **12** (200 mg, 0.55 mmol) and *tert*-butyl acrylate (240 μ l, 1.64 mmol) in benzene (40 cm³), under a nitrogen atmosphere. Triethylborane (1 M solution in tetrahydrofuran, 100 μ l, 0.10 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (40% petroleum ether–60% ethyl acetate) to give **17** as a 6.5:1 ratio of inseparable diastereoisomers (26 mg, 13%) as a yellow syrup (Found MH⁺ (ES⁺) 370.2250, C₂₂H₂₈DN₂O₃ requires 370.2241); ν_{\max} (thin film)/cm⁻¹ 3092–2773 (m) (C–H), 1726 (s) (C=O), 1593 (w), 1560 (w), 1456 (w), 1048 (w), 1367 (m), 1257 (m), 1153 (s), 1065 (w), 993 (w), 847 (w), 756 (s), 700 (w) and 667 (w); δ_{H} (400 MHz; CDCl₃; major diastereoisomer only) 1.41 (9H, s, (CH₃)₃C), 1.58 (2H, *ca* q, *J* = 7, CH₂CH₂CO₂tBu), 2.23 (2H, *ca* dt, *J* = 3, 7, CH₂CO₂tBu), 3.20 (1H, m, NCH), 3.64 (1H, *ca* dd, *J* = 6, 8, CHHO), 3.85 (2H, s, PhCH₂), 4.15 (1H, *ca* dd, *J* = 7.5 and 8, CHHO) and 7.18–8.48 (9H, complex, phenylCH and pyridineCH); δ_{C} (100 MHz; CDCl₃; major diastereoisomer) 28.1 ((CH₃)₃C), 29.1 (CH₂CH₂CO₂tBu), 32.0 (CH₂CO₂tBu), 58.7 (PhCH₂), 63.2 (NCH), 70.6 (CH₂O), 80.4 ((CH₃)₃C), 127.5, 128.4, 129.2 (phenylCH), 138.1 (phenyl *ipso*C) and 172.5 (C = O) (note: NCD and pyridine carbon signals not visible owing to dilute sample and line broadening, respectively); δ_{C} (100 MHz; CDCl₃; minor diastereoisomer) 28.1 ((CH₃)₃C), 29.7 (CH₂CH₂CO₂tBu), 32.6 (CH₂CO₂tBu), 51.5 (PhCH₂), 60.6 (NCH), 68.8 (CH₂O) and 127.3, 128.4, 128.8 (phenylCH) (note: other signals not visible owing to dilute sample); δ_{D} (61.4 MHz; CCl₄) 5.05 (0.87D, CD, major diastereoisomer) and 5.27 (0.13D, CD, minor diastereoisomer); *m/z* (EI) 369 (M⁺, 1%), 240 (33), 91 (100) and 57 (34); *m/z* (CI) 370 (MH⁺, 58%), 190 (10), 106 (20), 95 (100) and 80 (35).

N-(2-Iodobenzyl)pyrrolidine **18**¹⁹

2-Iodobenzyl bromide (1.75 g, 5.9 mmol) and *N,N*-diisopropylethylamine (4.00 cm³, 23.0 mmol) were added to a stirred solution of pyrrolidine (560 μ l, 6.7 mmol) in acetonitrile (16 cm³). After stirring for 48 h, the solvent was removed *in vacuo*

and the residue was partitioned between ethyl acetate (16 cm³) and water (24 cm³). The separated organic phase was washed with water (2 × 24 cm³) and aqueous sodium chloride solution (saturated, 24 cm³) before drying (magnesium sulfate), filtering and evaporation of the solvent *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient from 95% petroleum ether–5% ethyl acetate to 80% petroleum ether–20% ethyl acetate) to give **18** (1.38 g, 82%) as a colourless oil (Found MH⁺ (CI) 288.0244, C₁₁H₁₅N requires 288.0244); ν_{\max} (thin film)/cm⁻¹ 3086–2644 (s) (C–H), 1697 (w), 1584 (w), 1459 (m), 1436 (m), 1374 (w), 1348 (m), 1326 (w), 1239 (w), 1201 (w), 1147 (w), 1129 (w) 1012 (s), 881 (w), 749 (s) and 650 (w); δ_{H} (300 MHz; CDCl₃) 1.81 (4H, m, CH₂CH₂CH₂CH₂), 2.60 (4H, m, N(CH₂)₂), 3.70 (2H, s, ArCH₂), 6.93 (1H, *ca* dt, *J* = 3.0, 7.5, arylCH), 7.32 (1H, *ca* dt, *J* = 1.5, 6.0, arylCH), 7.47 (1H, *ca* dd, *J* = 3.0, 6.0, arylCH) and 7.82 (1H, dd, *J* = 1.5, 7.5, arylCH); δ_{C} (75 MHz; CDCl₃) 23.6 (CH₂CH₂CH₂CH₂), 54.1 (N(CH₂)₂), 64.4 (ArCH₂), 100.1 (arylCI), 128.0, 128.4, 129.8, 139.2 (arylCH) and 141.6 (aryl *ipso*C); *m/z* (CI) 288 (MH⁺, 73%), 162 (100), 70 (75) and 52 (23). All data consistent with literature values.¹⁹

***N*-Benzyl-2-deuteropyrrolidine (20) and *N*-(2-deuterobenzyl)pyrrolidine (21)**

Tributyltin deuteride (98 atom% D, 508 mg, 1.74 mmol) and 2,2'-azobisisobutyronitrile (81 mg, 0.49 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)pyrrolidine **18** (250 mg, 0.87 mmol) in benzene (15 cm³), under a nitrogen atmosphere. The reaction mixture was heated to reflux and three further aliquots of 2,2'-azobisisobutyronitrile (81 mg, 0.49 mmol) were added at 1, 3.5 and 5 h. Reflux was continued for a further 1 h, after which time, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 100% dichloromethane to 80% dichloromethane–20% ethyl acetate) to give a mixture of **20** and **21** (65 mg, 23%) in a 19:1 ratio as a colourless oil (Found MH⁺ (ES⁺) 163.1340, C₁₁H₁₅DN requires 163.1340); ν_{\max} (thin film)/cm⁻¹ 3073–2503 (s) (C–H, C–D), 1667 (w), 1496 (w), 1456 (m), 1214 (w), 754 (w) and 701 (m); δ_{H} (300 MHz; CDCl₃) 1.96–2.05 (4H, complex, CHDCH₂CH₂), 2.96–3.06 (3H, complex, CH₂NCHD), 4.00 (2H, s, PhCH₂), 7.36–7.42 (3H, complex, phenylCH) and 7.53–7.61 (2H, complex, phenylCH); δ_{C} (75 MHz; CDCl₃) 23.1, 23.2 (CHDCH₂CH₂), 53.00 (CHD), 53.3 (NCH₂CH₂), 129.0, 130.2 (phenylCH) and 132.8 (phenyl *ipso*C); δ_{D} (61.4 MHz; CH₂Cl₂) 2.87 (0.95D, s, NCHD) and 7.52 (0.05D, s, phenylCD) *m/z* (EI) 162 (M⁺, 20%), 161 ((M–H)⁺, 45), 92 (17), 91 (100), 85 (49), 77 (15), 71 (30), 65 (37), 43 (42) and 42 (31); *m/z* (CI) 163 (MH⁺, 100%), 108 (4), 91 (5), 85 (4), 73 (15) and 71 (6).

2,2-Dideuteropyrrolidine hydrochloride (22)

Lithium aluminium deuteride (98 atom% D, 1.23 g, 29.3 mmol) was added to a stirred solution of 2-pyrrolidinone **23** (1.00 g, 11.8 mmol) in tetrahydrofuran (15 cm³) at 0 °C, under a nitrogen atmosphere. The reaction mixture was heated at reflux for 14 h, after which time the solution was cooled in an ice bath and water (1.23 cm³), aqueous sodium hydroxide solution (15% w/v, 1.23 cm³) and water (3.7 cm³) were added sequentially. The result-

ing solution was extracted with dichloromethane (4 × 10 cm³) and the combined extracts were washed with hydrochloric acid (2 M, 3 × 30 cm³). The combined aqueous extracts were evaporated to dryness *in vacuo* to give **22** (0.80 g, 62%) as a pale brown, hygroscopic solid (Found M–HCl (EI) 73.0864, C₄H₇D₂N requires 72.0860); ν_{\max} (thin film)/cm⁻¹ 3600–3200 (s) (N–H), 3138–2488 (s) (C–H, C–D), 1664 (m), 1460 (w), 1304 (w), 1129 (w), 1080 (w) and 1030 (w); δ_{H} (300 MHz; CDCl₃) 1.95–2.13 (4H, complex, NCH₂CH₂CH₂), 3.29 (2H, br m, NCH₂) and 9.63 (2H, br s, ⁺NH₂); δ_{C} (75 MHz; CDCl₃) 24.6 (NCD₂CH₂), 24.4 (NCH₂CH₂), 44.5 (CD₂) and 45.0 (NCH₂); δ_{D} (61.4 MHz; H₂O) (s, 3.18 CD₂); *m/z* (EI) 73 (M–HCl, 100%).

***N*-(2-Iodobenzyl)-2,2-dideuteropyrrolidine (19)**

2-Iodobenzyl bromide (2.10 g, 7.1 mmol) and *N,N*-diisopropylethylamine (4.44 cm³, 25.5 mmol) were added to a stirred solution of 2,2-dideuteropyrrolidine hydrochloride **22** (700 mg, 6.4 mmol) in acetonitrile (20 cm³). After stirring for 14 h, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (20 cm³) and water (20 cm³) and the separated organic phase was washed with water (2 × 20 cm³) and aqueous sodium chloride solution (saturated, 20 cm³). After drying (magnesium sulfate), filtering and evaporation of the ethyl acetate *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient from 95% petroleum ether–5% ethyl acetate to 80% petroleum ether–20% ethyl acetate) to give **19** (970 mg, 53%) as a yellow oil (Found MH⁺ (CI) 290.0370, C₁₁H₁₃D₂NI requires 290.0369); ν_{\max} (thin film)/cm⁻¹ 3120–2642 (m) (C–H and C–D), 1583 (w), 1562 (m), 1460 (m), 1436 (m), 1363 (m), 1328 (m), 1305 (m), 1229 (w), 1205 (w), 1170 (m), 1134 (m), 1116 (m), 1044 (w), 1012 (s), 749 (s) and 651 (w); δ_{H} (300 MHz; CDCl₃) 1.82 (4H, complex, CH₂CH₂CD₂), 2.58 (2H, m, NCH₂CH₂), 3.67 (2H, s, ArCH₂), 6.94 (1H, *ca* dt, *J* = 3.0, 7.5, arylCH), 7.31 (1H, *ca* dt, *J* = 1.5, 6.0, arylCH), 7.44 (1H, *ca* dd, *J* = 3.0, 6.0, arylCH) and 7.82 (1H, dd, *J* = 1.5, 7.5, arylCH); δ_{C} (75 MHz; CDCl₃) 23.4, 23.6 (CH₂CH₂CD₂), 53.3 (CD₂), 54.1 (NCH₂CH₂), 64.4 (ArCH₂), 100.1 (arylCI), 128.0, 128.4, 129.8, 139.2 (arylCH) and 141.7 (aryl *ipso*C); δ_{D} (61.4 MHz; H₂O) (s, 3.18 CD₂); 2.65 (s, CD₂); *m/z* (EI) 289 (M⁺, 23%), 217 (22), 162 (12), 134 (12), 127 (10), 105 (10), 92 (30), 91 (50), 86 (100), 72 (18), 63 (15), 57 (12) and 44 (59); *m/z* (CI) 290 (MH⁺, 81%), 164 (85), 72 (100), 52 (61) and 44 (56).

***N*-Benzyl-2,2-dideuteropyrrolidine (24) and *N*-(2-deuterobenzyl)-2-deuteropyrrolidine (25)**

Reaction at 80 °C. Tributyltin hydride (240 µl, 0.89 mmol) was added to a degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in benzene (15 cm³) under a nitrogen atmosphere. The reaction mixture was heated to reflux and 2,2'-azobisisobutyronitrile (20 mg, 0.12 mmol) was added. Reflux was continued for a further 12 h, during which time, three further aliquots of 2,2'-azobisisobutyronitrile (10 mg, 0.12 mmol) were added after 1.5, 3 and 10 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a

3 : 1 ratio (62 mg, 55%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} 3500–3000 (s) (C–D), 2970–2900 (s) (C–H), 1642 (m), and 1475 (m); δ_{H} (300 MHz; CDCl_3) 1.70 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.45 (2.25H, m, NCH_2 , NCHD), 3.62 (2H, s, PhCH_2) and 7.13–7.35 (4.75H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) 22.3, 22.5 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 58.3 (NCH_2CH_2), 65.0 (PhCH_2), 128.2, 128.8 (phenylCH), 131.7 (phenyl *ipso*C) and 132.6 (phenylCH); δ_{D} (61.4 MHz; CHCl_3) 2.53 (1.73D, s, NCD_2 , NCHD) and 7.40 (0.27D, s, phenylCD); m/z (EI) 163 (M^+ , 54%), 162 (72), 161 (12), 92 (42), 91 (100), 86 (58), 85 (39), 72 (48) and 65 (58); m/z (CI) 164 (MH^+ , 100%), 163 (25) and 62 (14).

Reaction at 25 °C. Tributyltin hydride (300 μl , 1.12 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.86 mmol) in benzene (15 cm^3), under a nitrogen atmosphere at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a 12 : 1 ratio (81 mg, 58%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} as reported above; δ_{H} (300 MHz; CDCl_3) 1.73 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.45 (2.07H, m, NCH_2 , NCHD), 3.55 (2H, s, PhCH_2) and 7.15–7.28 (4.93H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) as reported above; δ_{D} (61.4 MHz; CHCl_3) 2.85 (1.92D, s, NCD_2 , NCHD) and 7.65 (0.08D, s, phenylCD); m/z (EI) 162 ($(\text{M}-\text{H})^+$, 100%), 134 (29), 92 (8), 91 (73), 85 (68), 71 (85) and 65 (66).

Reaction at –50 °C. Tributyltin hydride (250 μl , 0.93 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (210 mg, 0.73 mmol) in fluorobenzene (12 cm^3), under a nitrogen atmosphere, at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a 49 : 1 ratio (78 mg, 66%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} as reported above; δ_{H} (300 MHz; CDCl_3) 1.70 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.48 (2.00H, m, NCH_2 , NCHD), 3.55 (2H, s, PhCH_2) and 7.15–7.28 (5.00H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) as reported above; δ_{D} (61.4 MHz; CHCl_3) 2.75 (1.98D, s, NCD_2 , NCHD) and 7.60 (0.02D, s, phenylCD); m/z (EI) 162 ($(\text{M}-\text{H})^+$, 20%), 92 (10), 91 (30), 73 (30) and 57 (100); m/z (CI) 164 (MH^+ , 20%), 153 (30) and 113 (58).

***N*-Benzyl-2,2-dideutero-5-deuteropyrrolidine (**26**) and *N*-(2-deutero benzyl)-2,2-dideuteropyrrolidine (**27**)**

Reaction at 80 °C. Tributyltin deuteride (98 atom% D, 210 μl , 0.78 mmol) was added to a degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (170 mg, 0.59 mmol) in benzene (12 cm^3), under a nitrogen atmosphere. The reaction mixture was

heated to reflux and 2,2'-azobisisobutyronitrile (50 mg, 0.31 mmol) was added. Reflux was continued for a further 12 h, during which time three further aliquots of 2,2'-azobisisobutyronitrile (50 mg, 0.31 mmol) were added after 1, 3.5 and 10 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in a 1 : 2 ratio (56 mg, 58%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} 3500–3000 (w) (C–D), 2990–2900 (s) (C–H), 1665 (m) and 1494 (m); δ_{H} (300 MHz; CDCl_3) 1.73 (4H, $\text{NCHDCH}_2\text{CH}_2$), 2.43 (1.70H, m, NCHD , NCH_2), 3.54 (2H, s, PhCH_2) and 7.15–7.29 (4.30H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) 23.7, 23.8 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 54.2 (NCD_2), 54.6 (NCHDCH_2), 62.5 (PhCH_2), 127.4, 128.5, 128.7, 129.4 (phenylCH), 139.5 (phenyl *ipso*C); δ_{D} (61.4 MHz; CHCl_3) 2.45 (2.30D, s, NCD_2 , NCHD) and 7.28 (0.70D, s, phenylCD); m/z (EI) 165 (MH^+ , 20%), 164 (M^+ , 32), 163 ($(\text{M}-\text{H})^+$, 100), 162 (20), 136 (8), 135 (20), 134 (8), 92 (38), 91 (84), 86 (62), 73 (42), 72 (49) and 65 (50).

Reaction at 25 °C. Tributyltin deuteride (98 atom% D, 250 μl , 0.93 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in benzene (15 cm^3), under a nitrogen atmosphere at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in a 7 : 1 ratio (81 mg, 71%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} as reported above; δ_{H} (300 MHz; CDCl_3) 1.71 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.43 (1.15H, m, NCHD , NCH_2), 3.56 (2H, s, PhCH_2) and 7.16–7.28 (4.85H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) as reported above; δ_{D} (61.4 MHz; CHCl_3) 2.60 (2.87D, s, NCD_2 , NCHD) and 7.65 (0.13D, s, phenylCD); m/z (EI) 164 (MH^+ , 69%), 162 ($(\text{M}-\text{H})^+$, 75), 162 (27), 92 (72), 91 (100), 87 (75), 73.2 (43), 72 (38) and 65 (66).

Reaction at –50 °C. Tributyltin hydride (200 μl , 0.74 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in fluorobenzene (12 cm^3), under a nitrogen atmosphere at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in 7 : 1 ratio (62 mg, 55%) as a colourless oil; ν_{max} (thin film)/ cm^{-1} as reported above; δ_{H} (300 MHz; CDCl_3) 1.73 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.44 (1.15H, m, NCHD , NCH_2), 3.55 (2H, s, PhCH_2) and 7.15–7.28 (4.85H, complex, phenylCH); δ_{C} (75 MHz; CDCl_3) as reported above; δ_{D} (61.4 MHz; CHCl_3) 2.58 (2.88D, s, NCD_2 , NCHD) and 7.46 (0.12D, s, phenylCD); m/z (EI) 163 ($(\text{M}-\text{H})^+$, 30%), 162 (59), 92 (6), 91 (79), 86 (100), 72 (90) and 65 (58).

3-(*N*-Benzylpyrrolidin-2-yl)propanenitrile (28)

Tributyltin hydride (470 μ l, 1.75 mmol) and 2,2'-azobisisobutyronitrile (85 mg, 0.52 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)pyrrolidine **18** (250 mg, 0.87 mmol) and acrylonitrile (280 μ l, 4.25 mmol) in benzene (15 cm³), under a nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 90% dichloromethane–10% petroleum ether to 80%–20% dichloromethane) to give **28** (104 mg, 56%) as a colourless oil (Found MH⁺ (EI⁺) 215.1544, C₁₄H₁₉N₂ requires 215.1543); ν_{\max} (thin film)/cm⁻¹ 3122–2726 (s) (C–H), 2244 (m) (CN), 1686 (m), 1530 (w), 1495 (m), 1453 (s), 1425 (m), 1369 (m), 1210 (w), 1154 (w), 1125 (m), 1075 (w), 740 (m) and 700 (m); δ_{H} (300 MHz; CDCl₃) 1.47 (1H, m, pyrrolidine NCHCH_aH_b), 1.59–1.79 (3H, complex, pyrrolidine NCH₂CH_aH_b, CH₂CH₂CN), 1.89–2.06 (2H, complex, pyrrolidine NCHCH_aH_b, pyrrolidine NCH₂CH_aH_b), 2.19 (1H, *ca* q, *J* = 6.5, pyrrolidine NCH_aH_b), 2.41 (2H, m, CH₂CN), 2.62 (1H, m, NCH), 2.93 (1H, m, pyrrolidine NCH_aH_b), 3.29, 3.93 (2 \times 1H, AB, *J* = 12.0, PhCH₂) and 7.20–7.38 (5H, complex, phenylCH); δ_{C} (75 MHz; CDCl₃) 13.1 (CH₂CN), 22.4 (CH₂CH₂CN), 29.4 (NCH₂CH₂), 29.6 (CHCH₂), 53.4 (pyrrolidine NCH₂), 58.9 (PhCH₂), 120.3 (CN), 127.0, 128.3, 128.6 (phenylCH) and 139.2 (phenyl *ipso*C); *m/z* (CI) 215 (MH⁺, 100%), 160 (14), 123 (10) and 58 (15).

3-(*N*-Benzyl-2,2-dideuteropyrrolidin-2-yl)propanenitrile (29) and 3-(*N*-(2-deuterobenzyl)-2-deuteropyrrolidin-2-yl)propanenitrile (30)

Reaction at 80 °C. Tributyltin hydride (460 μ l, 1.71 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.87 mmol) and acrylonitrile (280 μ l, 4.25 mmol) in benzene (15 cm³), under a nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 90% dichloromethane–10% petroleum ether to 80%–20% dichloromethane) to give a mixture of **29** and **30** in a 3.2:1 ratio (29 mg, 15%) as a colourless oil (Found MH⁺ (ES⁺) 217.1667, C₁₄H₁₇D₂N₂ requires 217.1668); ν_{\max} (thin film)/cm⁻¹ 3104–2692 (s) (C–H, C–D), 2245 (m) (CN), 1604 (w), 1495 (m), 1453 (s), 1425 (m), 1368 (m), 1201 (m), 1181 (m), 1119 (m), 1028 (w), 739 (m) and 701 (m); δ_{H} (400 MHz; CDCl₃) 1.51 (1H m, pyrrolidine NCH(orD)CH_aH_b both products), 1.57–1.79 (3H, complex, pyrrolidine NCH(orD)₂CH_aH_b, CH₂CH₂CN both products), 1.82–2.03 (2H, complex, pyrrolidine NCH(orD)CH_aH_b, pyrrolidine NCH(or D)₂CH_aH_b both products), 2.19 (0.24H, q, *J* = 6.5, pyrrolidine NCH_aH_b minor product), 2.33, 2.45 (2 \times 1H, 2 \times m, CH₂CN both products), 2.62 (0.74H, m, NCH major product), 2.91 (0.24H, m, pyrrolidine NCH_aH_b minor product), 3.28, 3.91 (2 \times 1H, AB, *J* = 12, PhCH₂ both products) and 7.07–

7.42 (4.76H, complex, phenylCH both products); δ_{C} (100 MHz; CDCl₃; with DEPT editing) 13.6 (CH₂CN), 22.7 (CH₂CH₂CN), 29.8 (pyrrolidine NCD₂CH₂), 30.1 (pyrrolidine NCHCH₂), 54.7 (pyrrolidine NCH₂ minor product), 59.2 (PhCH₂), 62.7 (NCH) and 127.4, 128.7, 129.1 (phenylCH); δ_{D} (61.4 MHz; CH₂Cl₂) 2.15 (0.76D, s, pyrrolidine NCD_aD_b major product), 2.60 (0.24D, s, NCD minor product), 2.85 (0.76D, s, pyrrolidine NCD_aD_b major product) and 7.35 (0.24D, s, phenylCD minor product); *m/z* (EI) 216 (M⁺, 1%), 162 (98), 92 (37), 91 (100), 65 (17), 54 (12) and 41 (22); *m/z* (CI) 217 (MH⁺, 100%), 162 (8), 127 (3) and 52 (1).

Reaction at 25 °C. Tributyltin hydride (460 μ l, 1.71 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.87 mmol) and acrylonitrile (280 μ l, 4.25 mmol) in benzene (15 cm³), at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **29** and **30** in a 4.5:1 ratio (44 mg, 23%) as a colourless oil (Found MH⁺ (ES⁺) 217.1669, C₁₄H₁₇D₂N₂ requires 217.1668); ν_{\max} (thin film)/cm⁻¹ as reported above; δ_{H} (300 MHz; CDCl₃) 1.50 (1H m, pyrrolidine NCH(orD)CH_aH_b both products), 1.61–1.81 (3H, complex, pyrrolidine NCH(orD)₂CH_aH_b, CH₂CH₂CN both products), 1.85–2.05 (2H, complex, pyrrolidine NCH(orD)CH_aH_b, pyrrolidine NCH(or D)₂CH_aH_b both products), 2.19 (0.18H, q, *J* = 6.5, pyrrolidine NCH_aH_b minor product), 2.34, 2.46 (2 \times 1H, 2 \times m, CH₂CN both products), 2.62 (0.82H, m, NCH major product), 2.93 (0.18H, m, pyrrolidine NCH_aH_b minor product), 3.28, 3.92 (2 \times 1H, AB, *J* = 12, PhCH₂ both products) and 7.07–7.42 (4.82H, complex, phenylCH both products); δ_{C} (75 MHz; CDCl₃) 13.1 (CH₂CN), 22.2 (CH₂CH₂CN), 29.4 (pyrrolidine NCD₂CH₂), 29.6 (pyrrolidine NCHCH₂), 53.4 (pyrrolidine NCH₂ major product), 54.2 (pyrrolidine NCH₂ minor product), 58.8 (PhCH₂), 62.2 (NCH), 120.2 (CN), 126.9, 128.2, 128.6 (phenylCH) and 139.2 (phenyl *ipso*C); δ_{D} (61.4 MHz; CH₂Cl₂) 2.14 (0.82D, s, pyrrolidine NCD_aD_b major product), 2.60 (0.18D, s, NCD minor product), 2.85 (0.82D, s, pyrrolidine NCD_aD_b major product) and 7.35 (0.18D, s, phenylCD minor product); *m/z* (EI) 216 (M⁺, 1%), 215 ((M–H)⁺, 3), 162 (53), 92 (30), 91 (100) and 65 (11); *m/z* (CI) 217 (MH⁺, 100%), 162 (10), 127 (18) and 106 (21).

Reaction at –50 °C. Tributyltin hydride (390 μ l, 1.45 mmol) and 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (210 mg, 0.73 mmol) and acrylonitrile (280 μ l, 4.25 mmol) in fluorobenzene (13 cm³), at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2'-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **29** and **30** in a 5.7:1 ratio (89 mg, 56%) as a colourless oil (Found MH⁺ (ES⁺) 217.1667, C₁₄H₁₇D₂N₂ requires 217.1668); ν_{\max} (thin

film)/cm⁻¹ as reported above; δ_{H} (300 MHz; CDCl₃) 1.51 (1H m, pyrrolidine NCH(orD)CH_aH_b both products), 1.64–1.81 (3H, complex, pyrrolidine NCH(orD)₂CH_aH_b, CH₂CH₂CN both products), 1.87–2.06 (2H, complex, pyrrolidine NCH(orD)CH_aH_b, pyrrolidine NCH(orD)₂CH_aH_b both products), 2.21 (0.15H, q, J = 6.5, pyrrolidine NCH_aH_b minor product), 2.34, 2.47 (2 × 1H, 2 × m, CH₂CN both products), 2.63 (0.85H, m, NCH major product), 2.93 (0.15H, m, pyrrolidine NCH_aH_b minor product), 3.29, 3.94 (2 × 1H, AB, J = 12, PhCH₂ both products) and 7.17–7.35 (4.85H, complex, phenylCH both products); δ_{C} (75 MHz; CDCl₃) 13.1 (CH₂CN), 22.2 (CH₂CH₂CN), 29.4 (pyrrolidine NCD₂CH₂), 29.6 (pyrrolidine NCHCH₂), 54.3 (pyrrolidine NCH₂ minor product), 58.8 (PhCH₂), 62.3 (NCH), 120.3 (CN), 127.0, 128.3, 128.7 (phenylCH) and 139.3 (phenyl *ipso*C) - major product NCD and other signals or minor product not observed; δ_{D} (61.4 MHz; CH₂Cl₂) 2.15 (0.85D, s, pyrrolidine NCD_aD_b major product), 2.59 (0.15D, s, NCD minor product), 2.85 (0.85D, s, pyrrolidine NCD_aD_b major product) and 7.35 (0.15D, s, phenylCD minor product); m/z (EI) 216 (M⁺, 3%), 215 ((M–H)⁺, 5), 162 (100), 92 (24), 91 (83), 65 (10) and 40 (39); m/z (CI) 217 (MH⁺, 100%), 162 (10), 127 (8), 106 (6), 52 (18) and 77 (7).

3-Bromobut-3-enyl methanesulfonate (33)²³

Methanesulfonyl chloride (1.05 cm³, 13.6 mmol) was added dropwise to a stirred solution of 3-bromobut-3-en-1-ol **34** (1.70 g, 11.3 mmol) and triethylamine (1.82 cm³, 13.6 mmol) in dichloromethane (38 cm³) at 0 °C. After stirring for a further 1 h at this temperature, water (38 cm³) was added and the separated aqueous phase was extracted with dichloromethane (3 × 22 cm³). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **33** (2.33 g, 90%) as a pale yellow oil (Found MH⁺ (⁷⁹Br, CI) 228.9457, C₅H₁₀⁷⁹BrO₃S requires 228.9534); ν_{max} (thin film)/cm⁻¹ 3037–2832 (w) (C–H), 1632 (m) (C=C), 1468 (w), 1414 (w), 1355 (s), 1265 (w), 1227 (w), 1176 (s), 1145 (m), 1057 (w), 987 (m), 964 (m), 910 (m), 805 (m) and 734 (w); δ_{H} (300 MHz; CDCl₃) 2.81 (2H, t, J = 6.0, CH₂CH₂O), 3.00 (3H, s, CH₃), 4.35 (2H, t, J = 6.0, CH₂O), 5.54 (1H, d, J = 1.2, CHH=C) and 5.72 (1H, d, J = 1.2, CHH = C); δ_{C} (75 MHz; CDCl₃) 37.2 (CH₃), 40.7 (CH₂CH₂O), 66.7 (CH₂O), 120.4 (CH₂=C) and 127.5 (CH₂ = C); m/z (CI) 231 (MH⁺ (⁸¹Br), 3%), 229 (MH⁺ (⁷⁹Br), 3), 149 (13), 135 (98), 133 (100), 115 (21), 97 (12), 85 (10), 79 (10), 71 (4), 53 (7) and 51 (7). (Note: Although the preparation of **33** has been reported,²³ no isolation method or characterisation was presented.)

1-(3-Bromobut-3-enyl)-2,2-dideuteropyrrolidine (31)

Anhydrous potassium carbonate (1.000 g, 7.24 mmol) and 3-bromobut-3-enyl methanesulfonate **33** (686 mg, 3.00 mmol) were added sequentially to a stirred solution of 2,2-dideuteropyrrolidine hydrochloride **22** (395 mg, 3.60 mmol) in dry acetonitrile (15 cm³). After heating the stirred reaction mixture under reflux for 12 h, additional anhydrous potassium carbonate (500 mg, 3.62 mmol) was added and reflux was continued for a further 12 h. The solid was filtered off and washed with dichloromethane (2 × 15 cm³) and the combined filtrate/washings were evaporated to dryness *in vacuo*. The residue produced was purified by flash chromatography on silica gel (gradient from 100% chloroform

to 95% chloroform–5% methanol) to give **31** (175 mg, 28%) as a colourless oil (Found MH⁺ (⁷⁹Br, CI) 206.0505, C₈H₁₃⁷⁹BrD₂N requires 206.0508); ν_{max} (thin film)/cm⁻¹ 3022–2338 (s) (C–H and C–D), 1672 (w), 1629 (m) (C=C), 1448 (w), 1317 (w), 1292 (w), 1240 (w), 1158 (m) and 913 (w); δ_{H} (300 MHz; CDCl₃) 1.83 (4H, br complex, CD₂CH₂CH₂), 2.59–2.79 (6H, br complex, pyrrolidine NCH₂ and C(Br)CH₂CH₂), 5.46 (1H, s, CHH=C) and 5.68 (1H, s, CHH = C); δ_{C} (75 MHz; CDCl₃) 23.1, 23.4 (CD₂CH₂CH₂), 40.5 (C(Br)CH₂CH₂), 53.3 (CD₂), 54.1 (pyrrolidine NCH₂), 54.5 (C(Br)CH₂CH₂N), 118.0 (CH₂=C) and 131.5 (CH₂ = C); δ_{D} (61.4 MHz; CH₂Cl₂) 3.20 (CD₂); m/z (CI) 208 (MH⁺ (⁸¹Br), 100%), 206 (MH⁺ (⁷⁹Br), 98), 128 (25), 86 (24), 74 (10) and 52 (10).

(±)-5,5-Dideutero-1-methylhexahydro-(1H-pyrrolizine) hydrobromide (35) and (±)-1,7a-dideutero-1-methyl-hexahydro-1H-pyrrolizine hydrobromide (36)

A degassed solution of tributyltin hydride (250 μ l, 0.93 mmol) and 2,2'-azobisisobutyronitrile (6 mg, 0.04 mmol) in benzene (12 cm³) was added dropwise (*via* a syringe pump) to a degassed solution of 1-(3-bromobut-3-enyl)-2,2-dideuteropyrrolidine **31** (70 mg, 0.34 mmol) and 2,2'-azobisisobutyronitrile (6 mg, 0.04 mmol) in benzene (28 cm³), at reflux under a nitrogen atmosphere, over a period of 1 h. After a further 2 h at reflux, the solvent was removed *in vacuo* and thiophenol (112 μ l, 1.09 mmol) was added to the resulting residue. The crude product thus obtained was purified by flash chromatography on silica gel (75% petroleum ether–25% diethyl ether, then a gradient from 99% dichloromethane–1% methanol to 95% dichloromethane–5% methanol) to give a mixture of **35** and **36** in a 5.7:1 ratio (21 mg, 30%) as a colourless syrup (Found (MH–Br)⁺ (ES⁺) 128.1402, C₈H₁₄D₂N requires 128.1403; ν_{max} (thin film)/cm⁻¹ 3436 (br, m) (⁺N–H), 3122–2417 (s) (C–H), 1641 (w), 1460 (m), 1385 (w) and 1033 (w); δ_{H} (300 MHz; CDCl₃) 1.07 (3H, d, J = 7.0, CH₃), 1.60–1.80 (2H, complex, C(2)H and C(7)H), 1.89–2.21 (4H, complex, C(2)H, C(7)H and C(6)H₂), 2.50 (0.85H, m, C(1)H), 2.69 (0.15H, m, C(5)H), 3.01 (1H, dd, J = 7, 10, C(3)H), 3.57 (1H, m, C(3)H), 3.92 (0.15H, m, C(5)H) and 4.24 (0.85H, *ca* q, J = 9, C(7a)H) (Note: The ¹H NMR spectrum showed the presence of a small quantity (*ca* 9%) of 1-(but-3-enyl)-2,2-dideuteropyrrolidine hydrobromide **37**, with distinguishable resonances at 5.16 (1H, d, J = 8, CH=CH₂ *cis*), 5.17 (1H, d, J = 16, CH=CH₂ *trans*) and 5.73 (1H, m, CH = CH₂); δ_{D} (61.4 MHz; CH₂Cl₂) 2.47 (0.15D, s, C(1)D), 2.70 (0.85D, s, C(5)D), 3.88 (0.85D, s, C(5)D) and 4.20 (0.15D, s, C(7a)D); δ_{C} (75 MHz; CDCl₃) 13.4 (CH₃), 25.6 (C(6)), 25.7 (C(7)), 30.6 (C(2)), 34.6 (C(1)), 53.7 (C(3)) and 70.2 (C(7a)) (Note: C(5)D₂ not distinguishable.); m/z (CI) 128 (MH⁺ (–Br), 100%), 58 (10), 52 (51) and 44 (18).

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